

Identification of Mitochondrial-Related Genes as Potential Biomarkers for Docetaxel-Resistant Prostate Cancer

Docetaxel'e Dirençli Prostat Kanseri için Potansiyel Biyobelirteçler Olarak Mitokondriyal İlişkili Genlerin Tanımlanması

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Abstract

Objectives: Prostate cancer (PC) is the most common cancer among men worldwide and a significant cause of cancer-related deaths. Docetaxel (DX), a taxane-based chemotherapeutic agent, was the first treatment to exhibit substantial efficacy in the management of PC. This study aims to demonstrate the mitochondrial genes that are affected by DX in PC using bioinformatics analysis.

Materials and Methods: For bioinformatics analysis, mRNA microarray data from DX-sensitive PC cell lines (DU145) and DX-resistant cell lines (DU145-DR), corresponding to the study GSE36135, were retrieved from the *Gene Expression Omnibus* (GEO) database. Differentially expressed genes (DEGs) were analyzed and identified using the Transcriptome Analysis Console 4.0 (TAC). Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses were performed to pinpoint significant genes and biological pathways associated with DX therapy. Additionally, protein-protein interaction network analysis was conducted to identify critical proteins and interactions within these pathways.

Results: TAC applied criteria of an adjusted p-value <0.05 , (*false discovery rate-FDR* <0.05) and $|\log_2FC| >1.0$ to identify DEGs. The analysis revealed the upregulation of 515 genes and the downregulation of 608 genes in DX-treated cells compared to controls. Enrichment analysis of DEGs indicated their involvement in pathways such as metabolic pathways, pathways of neurodegeneration involving multiple diseases, biosynthesis of cofactors, chemical carcinogenesis mediated by reactive oxygen species, valine, leucine, and isoleucine degradation, carbon metabolism, and oxidative phosphorylation. Among these, *ALDH4A1*, *ALDH6A1*, *ALDH2*, *PCCB*, *GLS*, *GATM*, *GLS2*, *IDH2*, *SUCLG2*, *ECI2*, *GLDC*, *IVD*, *ALDH7A1*, *ACACA*, *ALDH5A1*, *NDUFS7*, *PCK2*, *ARG2*, *FDXR*, and *CPT1A* were identified as the most significant candidate genes.

Conclusion: This comprehensive bioinformatics analysis sheds light on the molecular mechanisms underlying DX's action and highlights potential targets for combination therapies, offering promising strategies to enhance treatment efficacy in PC.

Keywords: Prostate cancer, docetaxel, bioinformatics, gene expression omnibus, gene expression

Öz

Amaç: Prostat kanseri (PK) dünya çapında erkekler arasında en yaygın kanserdir ve kansere bağlı ölümlerin önemli bir nedenidir. Taksan bazlı bir kemoterapötik ajan olan docetaxel (DX), PK tedavisinde önemli etkinlik gösteren ilk tedavi olmuştur. Bu çalışma, biyoinformatik analiz kullanarak PK'de DX'ten etkilenen mitokondriyal genleri göstermeyi amaçlamaktadır.

Gereç ve Yöntem: Biyoinformatik analiz için, GSE36135 çalışmasına karşılık gelen DX'e duyarlı PK hücre hatlarından (DU145) ve DX'e dirençli hücre hatlarından (DU145-DR) mRNA mikroarray verileri Gene Expression Omnibus-GEO veri tabanından alınmıştır. Diferansiyel olarak ifade edilen genler (DEG'ler) Transkriptom Analiz Konsolu 4.0 (TAC) kullanılarak analiz edilmiş ve tanımlanmıştır. Docetaxel tedavisi ile ilişkili önemli genleri ve biyolojik yolları belirlemek için Gen Ontolojisi ve Kyoto Genler ve Genomlar Ansiklopedisi yol analizleri yapılmıştır. Ayrıca, bu yollardaki kritik proteinleri ve etkileşimleri belirlemek için protein-protein etkileşimi ağ analizi yapılmıştır.

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Bulgular: TAC, DEG'leri tanımlamak için düzeltilmiş p-değeri $<0,05$ ($p<0,05$) (*yanlış bulgu oranı-FDR $<0,05$*) ve $|\log_2FC| >1,0$ kriterlerini uygulamıştır. Analiz, DX ile tedavi edilen hücrelerde kontrollere kıyasla 515 genin yukarı regülasyonunu ve 608 genin aşağı regülasyonunu ortaya koymuştur. DEG'lerin zenginleştirme analizi, metabolik yollar, çoklu hastalıkları içeren nörodejenerasyon yolları, kofaktörlerin biyosentezi, reaktif oksijen türlerinin aracılık ettiği kimyasal karsinogenez, valin, lösin ve izolösin bozunması, karbon metabolizması ve oksidatif fosforilasyon gibi yollara dahil olduklarını göstermiştir. Bunlar arasında *ALDH4A1, ALDH6A1, ALDH2, PCCB, GLS, GATM, GLS2, IDH2, SUCLG2, ECI2, GLDC, IVD, ALDH7A1, ACACA, ALDH5A1, NDUFS7, PCK2, ARG2, FDXR* ve *CPT1A* en önemli aday genler olarak belirlenmiştir.

Sonuç: Bu kapsamlı biyoinformatik analiz, DX'in etkisinin altında yatan moleküler mekanizmalara ışık tutmakta ve kombinasyon tedavileri için potansiyel hedefleri vurgulayarak PK'de tedavi etkinliğini artırmak için umut verici stratejiler sunmaktadır.

Anahtar Kelimeler: Prostat kanseri, docetaxel, biyoinformatik, gen ekspresyonu omnibus, gen ekspresyonu

Introduction

Prostate cancer (PC) is the second most common cancer among men globally and the significant cause of cancer-related deaths in men (1,2). Androgen receptor (AR), a transcriptional factor essential for the development and spread of PC (3,4). The AR regulates numerous genes that are essential to the identity and behavior of PC cells (5). Depending on patient appropriateness, localized PC is generally treated with radiation or surgery. High-risk cases with locally progressed or high-grade tumors can induce distal metastases, the main cause of death connected to PC (4).

With the development of several treatments that increase overall survival, the treatment landscape for metastatic PC has undergone significant changes in recent years (6). Advancements in precision medicine have enabled the identification of distinct PC subtypes and genetic alterations that can predict the efficacy of specific treatments (1,7). These treatments include AR signaling inhibitors such as abiraterone acetate, enzalutamide, apalutamide, and darolutamide (8) as well as radioligand therapies like radium-223 and 177Lu-PSMA-617 (9,10). Patients with advanced PC initially respond remarkably well to androgen deprivation therapy. However, the treatment eventually selects for cancer cells that adapt to androgen deprivation, resulting in the development of castration-resistant PC (CRPC) (2,11). Patients with metastatic CRPC (mCRPC) face a reduced life expectancy, with a median overall survival of less than 2 years (2).

Over the past decade, treatment options for CRPC have significantly improved (10).

While AR inhibitors have greatly improved outcomes for metastatic PC, long-term use always results in treatment resistance as cancer cells adjust to androgen deprivation. As a consequence of this resistance, CRPC develops, necessitating the use of other treatment approaches such as chemotherapy with docetaxel (DX). DX chemotherapy elicits a good level of response as first-line treatment and provides a significant survival advantage in CRPC patients (12). DX, a taxane-based chemotherapeutic agent, was the first treatment to exhibit

substantial efficacy in the management of this mCRPC (13). It promotes the phosphorylation of Bcl-2 *in vitro*, leading to its functional inactivation and subsequent induction of apoptosis (14,15).

Unfortunately, the therapeutic response to DX is inevitably time-limited, as patients eventually experience disease progression due to acquired drug resistance (13). Although the mechanisms underlying the development of DX resistance in PC are not fully understood, previous studies have identified several contributing factors and pathways involved in resistance. These mechanisms include increased intracellular drug efflux mediated by adenosine triphosphate-binding cassette transporters, expression of β -tubulin isoforms/mutations, alterations in cell death pathways, including apoptosis and autophagy, mutations in β -tubulin, and dysregulated AR signaling (13).

In this study, it was focused on gene expression profiles in parental DX-sensitive PC cell lines (DU145) and selected DX-resistant cells (DU145-DR) cells. In the recent studies, bioinformatics analysis has become a popular tool for the analysis and identification of novel and potential biomarkers as therapeutic targets for various diseases. Therefore, we utilized bioinformatics tools to analyze target genes and the interaction networks among them, providing deeper insights into the mechanisms underlying DX resistance.

Materials and Methods

Analysis of Differentially Expressed Genes

GSE36135 was generated using microarray-based gene expression analysis, and 2 replicate data for DU145-DR resistant and DU145-DS susceptible cells were used. The statistical power of the dataset was assessed for its adequacy to detect gene expression differences between groups. Transcriptome Analysis Console 4.0 uses methods such as robust multi-array average (RMA) normalization, ANOVA-based statistical analyses, and false discovery rate (FDR) corrections to analyze data from Affymetrix microarray platforms. RMA or signal space transformation normalization is applied. Quality control analyses are performed. The difference in expression of genes between two groups (e.g., resistant vs. susceptible) is calculated.

Differential gene expression is determined by ANOVA or Student's t-test. FDR correction is applied to increase the reliability of p-value thresholds (e.g., $FDR < 0.05$).

In our study, RMA normalization was applied during the data analysis process, differential gene expression analysis was performed, and statistical correction was made so that $FDR < 0.05$.

Gene expression datasets (GSE36135), freely accessible, were acquired from Gene Expression Omnibus (<https://www.ncbi.nlm.nih.gov/geo/>). In each dataset, differentially expressed genes (DEGs) were selected based on $p < 0.05$, $FDR < 0.05$, and a log-fold change > 1 . Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using DAVID software.

Identification of Mitochondria-associated DEGs

Mitochondria-associated DEGs (MitoDEGs) were screened and identified by comparing DU145 control and DU145-DR cells. A total of 1,352 mitochondria-associated genes were obtained from the MitoCarta 3.0 database (<http://www.broadinstitute.org/mitocarta>). MitoDEGs were identified by cross-referencing the DEGs of interest from each dataset with the mitochondria-associated genes. The results were visualized using Venn diagrams generated with the MolBioTools platform (<https://molbiotools.com/listcompare>).

Analysis of Protein-protein Interactions

Protein-protein interaction (PPI) networks were constructed based on the MitoDEGs using the STRING database (<https://string-db.org/>). Hub-MitoDEGs were identified using Cytoscape software (version 3.8.1) through the CytoHubba (<https://apps.cytoscape.org/apps/cytohubba>) and MCODE (<https://apps.cytoscape.org/apps/mcode>) plugins.

For the protein interaction subnetworks identified via the MCODE plugin, the following parameter settings were used: Degree cut-off: 2, Maximum depth: 100, K-Core: 2, and Node score cut-off: 0.2. Subsequently, the CytoHubba plugin was employed to select hub genes within the PPI network with a Matthews correlation coefficient ≥ 60 . The results were combined, and the top ten hub-MitoDEGs were selected for further analysis.

Results

Analysis of DEGs

Comparisons were performed as DU145-DR vs. DU145; 608 genes with decreased expression and 515 genes with increased expression were identified.

Subsequently, these genes were cross-referenced with the list of 1,140 mitochondria-associated genes, and the number

of overlapping genes was identified as 59 and visualized accordingly (Figure 1).

Functional Enrichment Analysis of DEGs

To identify the biological properties of the DEGs, GO enrichment analysis was performed on 438 downregulated and 469 upregulated DEGs using DAVID online tools. Biological processes with at least 20 clustered genes and a p-value < 0.05 , $FDR < 0.05$ were considered significant. The analysis revealed that key enriched biological processes were primarily associated with chromatin remodeling, signal transduction, cell division, ATP activity, and protein kinase activity.

In the KEGG pathway analysis, the DEGs were found to be enriched in metabolic pathways, pathways of neurodegeneration-multiple diseases, biosynthesis of cofactors, chemical carcinogenesis-reactive oxygen species (ROS), valine, leucine and isoleucine degradation, carbon metabolism and oxidative phosphorylation (OXPHOS). Detailed results of the GO and KEGG pathway analyses are presented in Tables 1 and 2.

Construction of the PPI Network and Identification of Hub Genes

To investigate the interactions among DEGs and identify hub genes associated with DX resistance in PC, we utilized the STRING database to construct PPI networks. Subsequent analyses were performed using the CytoHubba plugin in Cytoscape software. Twenty hub genes were ranked based on their MCC scores, reflecting the number of gene interactions within the PPI network. *ALDH4A1*, *ALDH6A1*, *ALDH2*, *PCCB*, *GLS*, *GATM*, *GLS2*, *IDH2*, *SUCLG2*, *ECI2*, *GLDC*, *IVD*, *ALDH7A1*, *ACACA*, *ALDH5A1*, *NDUFS7*, *PCK2*, *ARG2*, *FDXR*, and *CPT1A* are among the hub genes which are upregulated and downregulated in DU145-DR compared to DU145 cells (Figure 2) (16).

Discussion

PC is the most common cancer among men worldwide and a leading cause of cancer-related deaths globally. DX has shown substantial efficacy in the management of PC, but its therapeutic response is limited, as patients inevitably develop resistance and disease progression (1,2,13). While the mechanisms underlying DX resistance in PC are not fully understood, several contributing factors and pathways have been identified (13). Still, there are studies which focus on the mechanisms involved in DX-resistance in PC.

Our bioinformatics analysis identified *ALDH4A1*, *ALDH6A1*, *ALDH2*, *PCCB*, *GLS*, *GATM*, *GLS2*, *IDH2*, *SUCLG2*, *ECI2*, *GLDC*, *IVD*, *ALDH7A1*, *ACACA*, *ALDH5A1*, *NDUFS7*, *PCK2*, *ARG2*, *FDXR*, and *CPT1A* as the most significant mitochondrial-related genes potentially implicated in DX resistance progression in PC. Moreover, our KEGG pathway analysis also reported the high

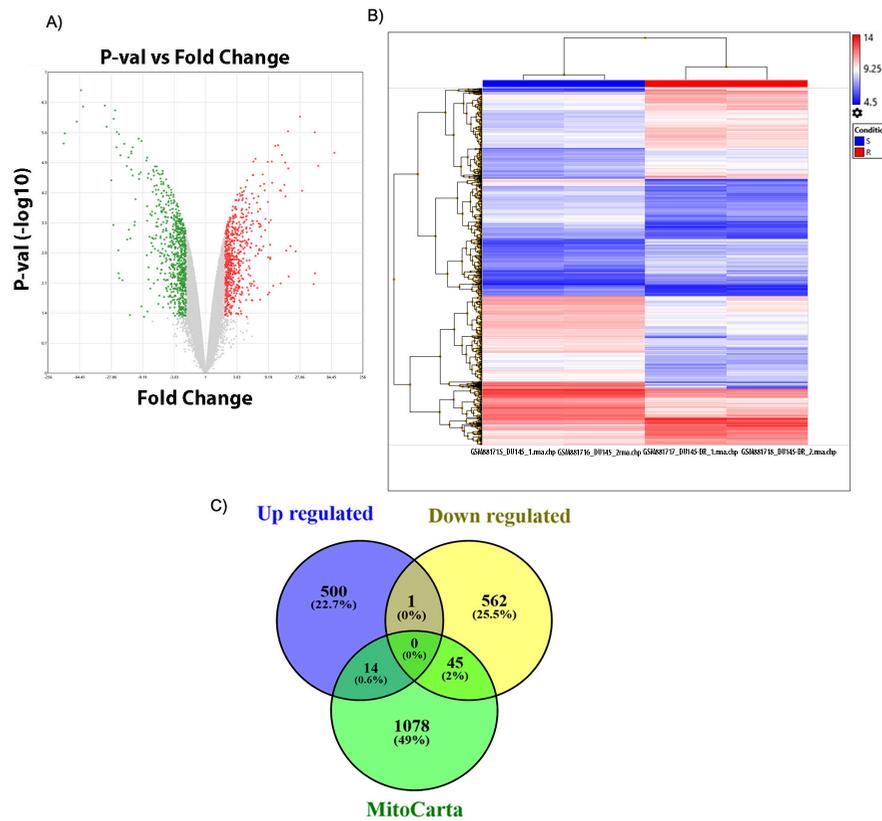


Figure 1: A) The number of DEGs identified in each comparison was recorded, and their distribution was visualized using volcano plots, (Green dots represent genes with decreased expression, while red dots indicate genes with increased expression); B) GSM881715_DU145_1, GSM881716_DU145_2 are Docetaxel-sensitive samples, and GSM881717_DU145-DR.1 and GSM881717_DU145-DR.2 are Docetaxel-resistant samples. The vertical axis is the DEG cluster, the horizontal axis is the sample cluster, the orange color represents up-regulated genes, and the blue color represents down-regulated genes; C) The intersecting upregulated and downregulated genes among groups obtained from Venn diagram
DEGs: Differentially expressed genes

Table 1: GO enrichment analysis of upregulated and downregulated genes (p<0.05) (FDR<0.05)			
Category	Term	Count	Genes
GOTERM_BP_DIRECT	GO:0009060~aerobic respiration	4	<i>OXA1L, NDUFA6, UOQCRB, UOQCR1</i>
	GO:0045333~cellular respiration	3	<i>UOQCRB, COX411, UOQCR1</i>
	GO:1902600~proton transmembrane transport	4	<i>NDUFA6, COX411, UOQCR1, SLC25A4</i>
GOTERM_CC_DIRECT	GO:0005759~mitochondrial matrix	21	<i>ARG2, ACSM3, GLDC, IDH2, MRPS10, LIAS, COASY, DHTKD1, GLS, GSTZ1, ALDH4A1, OXA1L, ALDH6A1, NFS1, ALDH5A1, ALDH2, IVD, ETHE1, PCCB, LONP1, BCL2L1</i>
	GO:0005743~mitochondrial inner membrane	11	<i>OXA1L, NDUFA6, UOQCRB, COX411, UOQCR1, MRPS10, SLC25A20, DNAJC15, SLC25A4, COQ6, BCL2L1</i>

GO: Gene Ontology, FDR: False discovery rate

number of genes enriched in the metabolic pathway, OXPHOS, carbon metabolism, and other sub-pathways of the metabolic pathway.

Recent studies reported that progression and resistance to treatment of PC are significantly affected by metabolic changes (17). Advanced-stage PC has been strongly linked to metabolic syndrome, a clinical condition defined by glucose intolerance, dyslipidemia, hypertension, and obesity (18). Both metabolic

syndrome and diabetes are commonly associated with more aggressive PC characteristics and poorer patient outcomes (17). Metabolic profiling in PC holds dual clinical potential: serving as a diagnostic tool for identifying aggressive PC and enabling the selection of predictive biomarkers for therapies that target metabolic pathways to inhibit cancer progression (17). The study carried out by Ippolito et al. (19) reported that DX-resistant PC3 cells (PC3-DR) exhibit enhanced invasiveness,

Category	Term	Count
KEGG_PATHWAY	hsa01100: Metabolic pathways	27
KEGG_PATHWAY	hsa05022: Pathways of neurodegeneration - multiple diseases	6
KEGG_PATHWAY	hsa01240: Biosynthesis of cofactors	5
KEGG_PATHWAY	hsa05208: Chemical carcinogenesis - reactive oxygen species	5
KEGG_PATHWAY	hsa00280: Valine, leucine and isoleucine degradation	4
KEGG_PATHWAY	hsa01200: Carbon metabolism	4
KEGG_PATHWAY	hsa00190: Oxidative phosphorylation	4

KEGG: Kyoto Encyclopedia of Genes and Genomes, FDR: False discovery rate

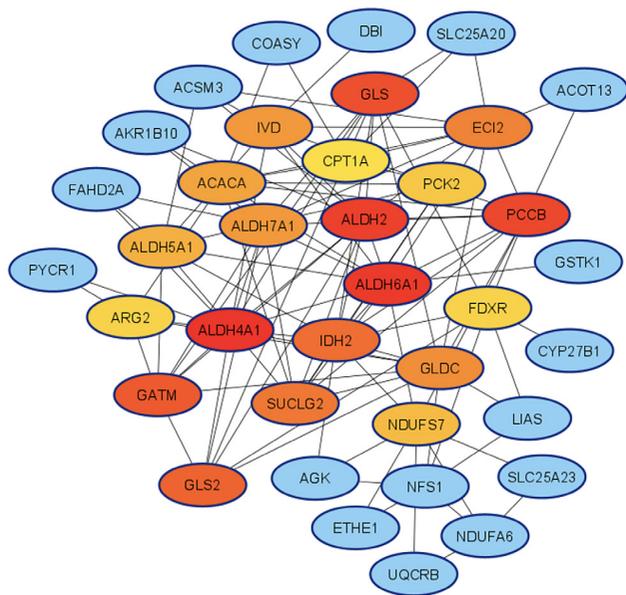


Figure 2: Top 20 hub genes screened by degree according to cytoHubba plug-in DU145-DR vs DU145 cells. The top 20 hub genes ranked by the MCC algorithm and their neighbors in the blue nodes. The red nodes represent genes with a high MCC score, while yellow nodes represent genes with a low MCC score

undergo epithelial-to-mesenchymal transition, and show reduced intracellular ROS and cell growth. Metabolic analysis indicates a shift toward a more efficient respiratory phenotype, utilizing glucose, glutamine (Gln), and lactate via mitochondrial OXPHOS (19).

Among these genes, *ALDH2* is the best-known isoform for converting acetaldehyde in alcohol metabolism (20). *ALDH2* has also been associated with the progression of various cancers. Decreased *ALDH2* expression has been observed in metastatic samples compared to primary PC and healthy prostate tissues (21). In studies investigating the biological mechanisms underlying lethal PC, *ALDH2* and *ALDH1A3* were found to be downregulated in lethal tumors (22). Feng et al. (23) identified *ALDH2* as a potential biomarker for predicting biochemical recurrence in PC patients and linked its expression to poor prognosis. Interestingly, *ALDH1A3*, *ALDH1B1*, and *ALDH2* mRNA

expressions were reported to be increased in malignant PC samples compared to benign prostatic hyperplasia (24). Another significant mitochondrial-related gene, *IDH2*, plays a vital role in citrate metabolism (25). Silencing *IDH2* in PC cells has been shown to impair oxidative bioenergetics and increase ROS production (26). *IDH1* and *IDH2* mutations are seen in 1-3% of patients with PC (25). In PC, two *IDH1* mutations (R132C and R132H) are common and are not associated with the stage or grade of PC (27,28). Inhibition of *IDH1* reduced the proliferation of PC cells *in vitro* and *in vivo*, and it has been reported that *IDH1* can be used as a target for the treatment of PC (29).

The role of *glutaminase (GLS)* in PC has also been extensively studied. *GLS*, which facilitates Gln degradation, is overexpressed in PC samples compared to benign prostatic hyperplasia and correlates with advanced pathological stages (30). *GLS*-dependent proliferation has been observed in PC3 PC cells, where its suppression reduces cell growth, intracellular ATP levels, and invasiveness (30). High levels of oxidative stress have been detected in C4-2B PC cells, which release large extracellular vesicles that may promote bone metastases (31). *GLS* inhibition in these cells decreases exosome release, highlighting the importance of Gln metabolism in metastatic PC (31).

Furthermore, suppression of *GLS* in DU145 and PC-3 cells induces apoptosis and cell cycle arrest by increasing Bax and decreasing cyclinD1 and Bcl-2 levels. This suppression also downregulates the Wnt/ β -catenin pathway, a critical pathway in cancer progression, making *GLS* a potential therapeutic target (32).

The role of *GLS* in PC is complex. Androgen depletion therapy suppresses the kidney-specific *GLS1* isoform while inducing the androgen-independent enzyme glutaminase C (GAC), which promotes cancer cell survival (33). Suppression of GAC has shown better therapeutic efficacy in testosterone-independent PC than in hormone-sensitive forms (33). Additionally, *GLS* overexpression has been linked to increased energy demands in radiotherapy-resistant PC and PC stem cells. Combining *GLS1* inhibition with radiotherapy and targeting Gln metabolism may improve treatment efficacy. However, as cancer cells can activate autophagy to survive Gln deficiency, the inclusion of autophagy inhibitors has also been suggested (34).

Although the exact processes underlying DX resistance are still unknown, a mesenchymal phenotype is linked to DX resistance (35). Since OXPHOS, which is largely driven by Gln, produces the majority of ATP, mesenchymal phenotypes have been associated with metabolic rewiring (35). In DX-resistant PC cells, Gln depletion and *GLS* suppression disrupt critical survival pathways, including OXPHOS and ATP production (35). In a study using cancer-associated fibroblasts together with PC cells by mimicking the tumor microenvironment, it was determined that fibroblasts metabolically reprogram cancer cells and *GLS* may be an important therapeutic target (36). In summary, mitochondrial-related genes such as *ALDH2*, *IDH2*, and *GLS* play crucial roles in PC progression and resistance mechanisms, particularly against DX.

In our study, although many genes have been shown to have different gene expression in prostate DX resistance, there are genes including *PCCB*, *GATM*, *IVD*, *ALDH5A1*, and *NDUS7*, which their roles in PC have not yet been studied.

In this study, the role of mitochondria-related genes identified by bioinformatic analyses in DX resistance was revealed. However, these findings need to be experimentally validated in the laboratory. Potential validation approaches include qPCR, Western blot, and functional assays.

In particular, qPCR can be used to measure the expression levels of selected genes in different cell lines and test the accuracy of bioinformatic analyses. By examining the changes in the protein levels of these genes with Western blotting, it can be evaluated how the differences at the transcript level are reflected at the protein level.

In addition, using functional assays (e.g., cell viability assays, invasion, and apoptosis assays), the effects of the identified genes on DX resistance can be directly observed. Specifically, the changes in the drug resistance profiles of cells when these genes are silenced or overexpressed should be analyzed.

Conclusion

The findings of this study highlight the potential of targeting specific genes through silencing or upregulating their expression as a promising approach for PC therapy. In future studies, the implementation of the experimental validation steps will contribute to the identification of new therapeutic targets, increasing the validity of bioinformatics findings in a clinical context. It is also important to integrate these genes with clinical data to determine their prognostic or predictive value in patients.

Ethics

Ethics Committee Approval: Not applicable. This paper does not involve human or animal subjects.

Informed Consent: Not applicable. This paper does not involve human or animal subjects.

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